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<b>(21) International Application Number:</b> PCT/US98/12273 <b>(22) International Filing Date:</b> 12 June 1998 (12.06.98)  <b>(30) Priority Data:</b> 08/874,033 12 June 1997 (12.06.97) US  <b>(71)(72) Applicant and Inventor:</b> BRASWELL, A., Glenn [US/US]; Suite 400, 6100 Lake Forrest Drive, N.E., Atlanta, GA 30328 (US).  <b>(72) Inventor:</b> AHMED, Aftab, J.; 14122-A Marquesas Way, Marina Del Rey, CA 90292 (US).  <b>(74) Agents:</b> OLIFF, James, A. et al.; Oliff & Berridge, PLC, P.O. Box 19928, Alexandria, VA 22320 (US).		<b>(81) Designated States:</b> JP, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).  <b>Published</b> <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
<b>(54) Title:</b> WEIGHT CONTROL COMPOSITION COMPRISING HYPERICUM PERFORATUM  <b>(57) Abstract</b>  A method of controlling weight in mammals by orally administering to the mammal an amount of a pharmaceutical composition containing <i>Hypericum perforatum</i> or active components thereof effective to control the weight of the mammal is described. The pharmaceutical composition also preferably further contains at least one thermogenic agent and at least one agent inhibiting lipogenesis. The at least one thermogenic agent includes one or more of N-acetyl-L-carnitine, cayenne extract, inositol hexanicotinate, niacin or salicin. The at least one agent inhibiting lipogenesis may be hydroxy citric acid. When the pharmaceutical composition includes <i>Hypericum perforatum</i> , at least one thermogenic agent and at least one agent inhibiting lipogenesis, the composition acts to control the weight of the mammal by simultaneously suppressing appetite, inducing thermogenesis and inhibiting lipogenesis.		

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## WEIGHT CONTROL COMPOSITION COMPRISING HYPERICUM PERFORATUM

BACKGROUND OF THE INVENTION1. Field of the Invention

5 This invention relates to a pharmaceutical composition and method of administering the same to a mammal, which pharmaceutical composition acts to control the weight of the mammal. More specifically, the composition acts to at least suppress appetite, and  
10 preferably also acts to induce thermogenesis and inhibit lipogenesis, so as to prevent weight gain and/or facilitate weight loss.

2. Discussion of Related Art

Serotonergic neurons control the release of  
15 neurotransmitters as a function of food uptake. It is well established that carbohydrate consumption increases serotonin release whereas protein ingestion does not. Biochemically, dietary starch is degraded to sugar which stimulates the pancreas to release insulin. Insulin, in  
20 turn, raises the levels of tryptophan in the brain. Tryptophan is a precursor of serotonin, and serotonin affects the mood. Neuronal signaling in food consumption, thus, provides a feedback mechanism to maintain a balance between protein and carbohydrate ingestion. Serotonin,  
25 however, also affects several other loci in the central nervous system which control, for example, sleep, pain sensitivity, libido, satiety center, maintenance of optimal blood pressure and mood. See, for example, Wurtman et al., "Brain Serotonin, Carbohydrate-Craving, Obesity and  
30 Depression," Obesity Research, Volume 3, Supplement 4, pages 477S-480S (1995). Thus, obese people tend to binge on carbohydrates, which is a common cause of weight gain. People exposed to stress, people in depression and ex-smokers trying to disabuse themselves of nicotine  
35 habituation also have a tendency to gain weight. In short,

there is a clinical link between serotonin, dietary habits, obesity and depression. See Wurtman et al., supra.

It has been known to use certain anti-depressants as weight control agents. For example, Prozac™ has been known to be used as a weight control agent. However, as well documented, Prozac has several undesirable side effects. It is therefore desired to develop a weight control composition that is free of undesirable side effects.

*Hypericum perforatum*, also known as St. John's wort, has been known to be used in treatments to remedy depression, anxiety, mania, hypochondriasis and fatigue. See, for example, Murray, "The Healing Power of Herbs," 2<sup>nd</sup> Edition, pages 294-301 (1995); Castleman, "The Healing Herbs," pages 321-325 (1991); Harrer et al., "Treatment of Mild/Moderate Depressions With *Hypericum*," *Phytomedicine*, Volume 1, pages 3-8 (1994); and De Smet et al., "St. John's wort As An Antidepressant," *BMJ London*, August 3, 1996. The major active compounds of interest in *Hypericum perforatum* are hypericin and pseudohypericin. *Hypericum perforatum* has the effect of inhibiting serotonin uptake by synaptosomes, thereby increasing the amount of serotonin in the system. This increase in the serotonin level contributes to the anti-depressant activity of *Hypericum perforatum*. See, for example, Perovic et al., "Pharmacological Profile of *Hypericum* Extract," *Drug Research*, Volume 45 (II), No. 11, pages 1145-1148 (1995). *Hypericum perforatum* is often reported to have no notable side effects (Harrer et al., supra), or very minor side effects, such as gastrointestinal symptoms, allergic reactions and/or fatigue (De Smet et al., supra), as well as reduced appetite. *Hypericum perforatum* has also been reported to result in an increased appetite (Castleman, supra).

Although *Hypericum perforatum* is known for use as an anti-depressant, it has not been specifically used as an agent for weight control. Serezac™ is a commercially

available product containing *Hypericum perforatum*. Serezac is marketed and administered as an anti-depressant.

The majority of commercially available weight control products focus upon only one avenue of weight control, most typically appetite suppression. This avenue seeks to regulate food intake through drug administration directed to one or more systems known to play a role in food digestion. See, for example, Sullivan et al., "Mechanisms of Appetite Modulation By Drugs," Federation Proceedings, Volume 44, No. 1, Part 1, pages 139-144 (1985). Regulation of serotonin level is one such method of appetite suppression.

However, thermogenesis and inhibiting lipogenesis are other avenues of weight control. Thermogenesis is the major mechanism by which the body burns the metabolically active brown fat. Brown fat cells are a part of the sympathetic nervous system, and serve as a locale for the release of norepinephrine, which triggers thermogenesis. Thermogenesis prevents the storage of dietary lipids while also converting stored fat into soluble lipids that are burnt off by the body to generate energy.

Lipogenesis is a process in which excess glucose is converted into fat and stored in adipose tissues throughout the body. Inhibiting this process, for example by binding a material to the enzyme citrate lyase to reduce the production of fat and cholesterol, can act to reduce weight gain and/or induce weight loss.

#### SUMMARY OF THE INVENTION

It is an object of the present invention to develop a pharmaceutical composition that can effectively act to control the weight of a mammal to which the composition is administered. It is a further object of the present invention to develop a weight control pharmaceutical composition that can act to control the weight of a mammal to which the composition is administered through each of suppressing appetite, inducing thermogenesis and inhibiting

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lipogenesis. It is a still further object of the present invention to develop a method of administering a pharmaceutical composition to control weight without notable side effects.

5           These and other objects are achieved by a method of administering a pharmaceutical composition containing *Hypericum perforatum* or the active components thereof to a mammal, preferably a human, in a manner effective to control the weight of the mammal. In the method, the  
10       pharmaceutical composition is preferably administered orally. These objects are also achieved by a weight control pharmaceutical composition containing at least *Hypericum perforatum* or the active components thereof, a thermogenic agent and an agent inhibiting lipogenesis,  
15       preferably also with a pharmaceutically acceptable carrier.

#### DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

          The pharmaceutical composition capable of controlling the weight of a mammal to which the composition is administered comprises at least *Hypericum perforatum* or  
20       the active components thereof, and also preferably includes a thermogenic agent and/or an agent inhibiting lipogenesis. The pharmaceutical composition also preferably includes a pharmaceutically acceptable carrier.

          As mentioned above, *Hypericum perforatum*, also known  
25       as St. John's wort, contains both hypericin and pseudohypericin as active components. The composition and method of the invention preferably utilizes an extract of *Hypericum perforatum*. However, rather than an extract, hypericin and/or pseudohypericin may be used alone or  
30       together in the composition. Within the system of a mammal such as a human, *Hypericum perforatum* extract, as well as hypericin and pseudohypericin, functions essentially as a monoamine oxidase inhibitor, and, as such, increases the concentration of serotonin in synaptosomes by inhibiting  
35       the re-uptake of serotonin in the system. Serotonin release is increased when the mammal intakes carbohydrates.

Serotonin thus has a satiety promoting effect in the system which regulates against the over consumption of carbohydrate-rich foods. As such, because *Hypericum perforatum* increases the quantity of serotonin present  
5 within synaptosomes, it can act to reduce the desire to consume carbohydrate-rich foods, i.e., it can act to suppress the appetite of the mammal.

A major advantage to the inclusion of *Hypericum perforatum* in a pharmaceutical composition to be  
10 administered as a weight controlling agent is that this active compound exhibits no notable side effects. In this respect, *Hypericum perforatum* is desired over other monoamine oxidase inhibitors such as Prozac that has a well documented history of adverse side effects.

15 According to one embodiment of the invention, a pharmaceutical composition containing *Hypericum perforatum*, preferably also containing a pharmaceutically acceptable carrier, is administered to a mammal in dosages effective to control the weight of the mammal. The weight  
20 controlling function of the composition containing *Hypericum perforatum* is believed to occur through appetite suppression as a result of an increase in the serotonin level in synaptosomes.

In another embodiment of the invention, the  
25 pharmaceutical composition preferably further contains a thermogenic agent, i.e., an agent inducing thermogenesis. Thermogenesis is the major mechanism by which the body burns metabolically active brown fat. Thermogenesis prevents the storage of dietary lipids and also converts  
30 stored fat into soluble lipids that are burnt off by the mammal. As such, a thermogenic agent can act to control and reduce the weight of a mammal to which the composition containing the thermogenic agent is administered.

Any thermogenic agent, or mixture of agents, known  
35 in the art may be used. For example, the thermogenic agent may include one or more of kola nut, N-acetyl-L-carnitine,

cayenne extract, salicin, niacin or inositol hexanicotinate.

While kola nut is a useful thermogenic agent, it contains caffeine which can cause nervousness and mild agitation so that kola nut is a less desired thermogenic agent, particularly when administered in higher amounts. N-acetyl-L-carnitine is very useful in facilitating the transport of fat into mitochondria for their metabolization to generate energy. Cayenne extract stimulates the production of energy in the form of adenosine triphosphate (ATP) which, in turn, metabolizes more fat. Salicin, which is found naturally in the bark of the white willow, also has been implicated in the stimulation of thermogenesis.

Niacin, also known as vitamin B-3, is known to induce thermogenesis and acts to lower low density lipoprotein (LDL) cholesterol levels and elevate high density lipoprotein (HDL) cholesterol levels. It does so by reducing lipoprotein synthesis in the liver. See, for example, Stone, "Lipid Management: Current Diet Drug Treatment Options," The American Journal of Medicine, Volume 101, Supplement 4A, pages 40S-49S (1996). Niacin, however, can have severe undesirable side effects, the most common of which is a prostaglandin-mediated flush.

A safer form of niacin in terms of reduced side effects is inositol hexanicotinate. Inositol hexanicotinate consists of six (6) molecules of niacin conjugated to one (1) molecule of inositol. The compound is slowly metabolized within the mammalian system to niacin and inositol. Inositol hexanicotinate is thus referred to as a "sustained-release" or "time-release" niacin in that niacin administered in the form of this compound is present within the system over a longer period of time compared to niacin administered alone.

Another form of niacin that might be suitably administered is the so called "no-flush" niacin that is complexed with chromium, and is commercially available.



If niacin, inositol hexanicotinate or other forms thereof are included in the pharmaceutical composition, the composition preferably also further includes a vitamin B-6 compound. The vitamin B-6 compound enhances the effect of  
5 the vitamin B-3 compound, i.e., it enhances the thermogenic effect. A most preferred vitamin B-6 compound to use in conjunction with, for example, inositol hexanicotinate, is pyridoxyl phosphate.

The pharmaceutical composition also preferably  
10 further includes an agent capable of inhibiting lipogenesis. Lipogenesis is a process in which carbohydrates and excess glucose are converted into fat for storage in adipose tissues throughout the body. Lipogenesis thus results in weight gain. Agents that can  
15 inhibit the process of lipogenesis thus can also effectively act to control the weight of a mammal.

The conversion of carbohydrate into fat involves the oxidation of pyruvate to acetyl-CoA. Pyruvate oxidation is an intramitochondrial process while fatty acid synthesis is  
20 predominantly an extramitochondrial process. The acetyl group of intramitochondrial acetyl-CoA must therefore be diverted from the intramitochondrial to the extramitochondrial compartment of a cell before it can be converted into fatty acids. This transfer takes place in  
25 the form of citrate. Any agent that interferes in this lipogenic process can be suitably added to the pharmaceutical composition.

A most preferred agent for inhibiting lipogenesis is hydroxycitric acid or hydroxy citrate. This material is a  
30 powerful inhibitor of ATP:citrate lyase, the enzyme which catalyzes the extramitochondrial cleavage of citrate to acetyl-CoA and oxaloacetate. In other words, hydroxy citric acid inhibits lipogenesis by tightly binding to the enzyme ATP:citrate lyase so as to reduce the production of  
35 fat and cholesterol in the system. See, for example, Watson et al., "Citrate and the Conversion of Carbohydrate

into Fat," The Journal of Biological Chemistry, Volume 245, No. 22, pages 5993-6002 (1970); Rao et al., "Lipid-Lowering and Antiobesity Effect of (-)Hydroxycitric Acid," Nutrition Research, Vol. 8, pages 209-212 (1988); Hellerstein et al.,  
5 "The Indirect Pathway of Hepatic Glycogen Synthesis and Reduction of Food Intake by Metabolic Inhibitors," Life Sciences, Volume 53, pages 1833-1845 (1993); and, Sullivan et al., "Factors Influencing the in vivo and in vitro Rates of Lipogenesis in Rat Liver," J. Nutrition, Volume 101,  
10 pages 265-272 (1971).

The enzyme ATP:citrate lyase is important in maintaining the acetyl-CoA pool for fatty acid and cholesterol synthesis. Inhibition of this enzymatic reaction limits the availability of 2-carbon units for  
15 fatty acid and cholesterol synthesis. Fatty acid synthesis is thus reduced without altering protein levels. It is believed that hydroxy citric acid reduces food consumption by diverting carbohydrates and fatty acids that would have become fat inside the liver into hepatic glycogen  
20 synthesis, which in turn sends a signal to the brain that results in reduced food intake.

Hydroxy citric acid is found naturally in the herb *Garcinia cambogia*, also known as "Malabar Tamarind."

A pharmaceutical composition containing the  
25 *Hypericum perforatum*, the thermogenic agent and an agent inhibiting lipogenesis is believed to control the weight of a mammal to which the composition is administered by simultaneously suppressing the mammal's appetite, inducing thermogenesis and inhibiting lipogenesis in the mammal's  
30 system. In this manner, the mammal does not desire to intake further food, existing stored fat is more readily burned off, and new sources of potential fat are prevented from forming fat.

The pharmaceutical compositions according to the  
35 invention also preferably include a pharmaceutically acceptable carrier. The pharmaceutical composition

preferably takes the form of solid tablets and/or capsules suitable for oral administration, although liquid formulations are also possible. The composition may be prepared into a form suitable for oral administration by  
5 any conventional method known to the art.

Any carriers known in the art for oral application compositions may be used. For solid form preparations, such as, for example, powders, tablets, disbursable granules and capsules, a solid carrier may be one or more  
10 substances such as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, tablet disintegrating agents, encapsulating materials and the like. Suitable carrier materials may include, for example, magnesium carbonate, calcium carbonate, sodium  
15 bicarbonate, magnesium stearate, calcium stearate, talc, lactose, sugar, pectin, dextrin, starch, tragacanth, cellulose derivatives, methyl cellulose, sodium carboxymethyl cellulose, a low-melting wax, cocoa butter, alginates, gelatin, polyvinyl pyrrolidone, polyethyl  
20 glycols, quaternary ammonium compounds and the like.

Liquid form preparations include solutions, suspensions and emulsions. Suitable carriers may include, for example, water, coloring, flavoring agents, stabilizers and thickening agents. Viscous materials, such as natural  
25 synthetic gums, resins, methyl cellulose, sodium carboxymethyl cellulose and other agents known to the pharmaceutical art may also be used.

The composition to be administered may be prepared in accordance with any dose preparation method known in the  
30 art, for example mixing, encapsulation, etc., and is not limited. The components of the composition may be added in any order without limitation. The *Hypericum perforatum* is preferably prepared for addition to the composition by, for example, grinding, comminuting, etc. the leaves and forming  
35 an extract by any known method, for example an aqueous or

organic extract. The extract is preferably standardized to 10% hypericin/pseudohypericin.

Additional materials may also be present in the pharmaceutical composition. For example, the composition may also contain L-phenylalanine, an amino acid that is the precursor of tyrosine which is required for the synthesis of the neurotransmitters epinephrine, norepinephrine and dopamine. L-tyrosine itself may also be present in the pharmaceutical composition.

The pharmaceutical composition may further include tryptophan, or more preferably 5-hydroxy tryptamine (5HT). Tryptophan is a precursor of serotonin. Other conventional materials such as calcium carbonate and magnesium oxide may also optionally be included within the pharmaceutical composition.

One dose of the pharmaceutical composition, for example one tablet or capsule, may contain, for example, 50 to 500 mg, preferably 100 to 250 mg, *Hypericum perforatum* standardized to hypericin. If the composition further contains thermogenic agent(s) and/or agent(s) inhibiting lipogenesis, the composition may contain, for example, 100 to 1,000 mg, preferably 150 to 500 mg, of thermogenic agent(s), and/or 50 to 500 mg, preferably 100 to 250 mg, of agent(s) inhibiting lipogenesis. A single dose of the pharmaceutical composition containing such amounts of active ingredients is most preferably administered in a total amount of two to four tablets per day to the mammal. The total amount of active ingredients within one dose of the pharmaceutical composition may be between, for example, 100 and 1,500 mg, preferably 250 to 1,250 mg, most preferably around 1000 mg.

The total daily amount of *Hypericum perforatum* administered to the mammal may be, for example, 100 to 2,000 mg. The total daily amount of thermogenic agent(s) administered may be, for example, 100 to 2,000 mg. The total daily amount of agent(s) inhibiting lipogenesis

administered may be, for example, 100 to 1,000 mg. The composition is preferably administered in spaced dosages throughout the day, for example administered every three to six hours, so as to maintain the level of active ingredients in the system of the mammal. As mentioned above, the doses are preferably administered orally so as to directly introduce the active ingredients into the digestive system of the mammal.

When inositol hexanicotinate is included in the pharmaceutical composition, pyridoxyl phosphate is preferably also included. Such composition is preferably administered in amounts such that the inositol hexanicotinate is administered in a total daily amount of, for example, 250 to 1,000 mg and pyridoxyl phosphate is administered in a total daily amount of 100 to 500 mg.

In a most preferred embodiment, the pharmaceutical composition comprises, for example, *Hypericum perforatum* in an amount of 150 mg, standardized to hypericin, *Garcinia cambogia* (hydroxy citric acid) in an amount of 150 mg, standardized to 10% hydroxy citric acid, inositol hexanicotinate in an amount of 450 mg (which corresponds to 350 mg basal niacin), pyridoxyl phosphate in an amount of 50 mg, and white willow bark extract (salicin) in an amount of 150 mg for a one dose formulation, for example, one tablet or capsule. This most preferred pharmaceutical composition is preferably administered a total of, for example, two to four times daily.

When the pharmaceutical composition is administered to a mammal, preferably a human, the composition controls the weight of the mammal so that preferably weight gain does not occur and more preferably, weight loss occurs.

What is claimed is:

1. A method of controlling weight in a mammal ,  
comprising orally administering to the mammal an amount of  
a pharmaceutical composition effective to control the  
5 weight of the mammal, the pharmaceutical composition  
comprising *Hypericum perforatum*.
2. A method according to Claim 1, wherein the  
pharmaceutical composition further comprises a  
pharmaceutically acceptable carrier.
- 10 3. A method according to Claim 1, wherein the  
pharmaceutical composition is administered in an amount  
such that the total daily amount of *Hypericum perforatum*  
administered ranges from 100 to 2,000 mg, standardized to  
hypericin.
- 15 4. A method according to Claim 1, wherein the  
pharmaceutical composition is administered in an amount of  
two to four single doses per day.
5. A method according to Claim 1, wherein the  
pharmaceutical composition is administered in tablet or  
20 capsule form, and wherein each tablet or capsule contains  
between 100 and 1,500 mg of active ingredients.
6. A method according to Claim 1, wherein the  
pharmaceutical composition further comprises inositol  
hexanicotinate and pyridoxyl phosphate such that the  
25 inositol hexanicotinate is administered in a total daily  
amount of from 250 to 1,000 mg and pyridoxyl phosphate is  
administered in a total daily amount of from 100 to 500 mg.
7. A method according to claim 1, wherein the  
pharmaceutical composition further comprises at least one  
30 thermogenic agent and at least agent inhibiting  
lipogenesis.
8. A method according to claim 7, wherein the  
pharmaceutical composition is administered in an amount  
such that the total daily amount of thermogenic agent  
35 administered ranges from 100 to 2,000 mg and the total

daily amount of the agent inhibiting lipogenesis administered ranges from 100 to 1,000 mg.

9. A method according to Claim 7, wherein the method controls the weight of the mammal by suppressing appetite, inducing thermogenesis and inhibiting lipogenesis.

10. A method of controlling weight in a mammal, comprising orally administering to the mammal an amount of a pharmaceutical composition effective to control the weight of the mammal, the pharmaceutical composition comprising one or both of hypericin and pseudohypericin.

11. A pharmaceutical composition, the pharmaceutical composition comprising *Hypericum perforatum*, at least one thermogenic agent and at least one agent inhibiting lipogenesis.

12. A pharmaceutical composition according to Claim 11, wherein the thermogenic agent comprises one or more of N-acetyl-L-carnitine, cayenne extract, inositol hexanicotinate, niacin and salicin.

13. A pharmaceutical composition according to Claim 12, wherein the salicin is derived from white willow bark extract.

14. A pharmaceutical composition according to Claim 11, wherein the agent inhibiting lipogenesis is hydroxy citric acid.

15. A pharmaceutical composition according to Claim 14, wherein the hydroxy citric acid is derived from *Garcinia cambogia*.

16. A pharmaceutical composition according to Claim 11, wherein the pharmaceutical composition further comprises a pharmaceutically acceptable carrier.

17. A pharmaceutical composition according to Claim 11, wherein the *Hypericum perforatum* is present in an amount of 50 to 500 mg, standardized to hypericin, the at least one thermogenic agent is present in an amount of 100

to 1,000 mg, and the at least one the agent inhibiting lipogenesis is present in an amount of 50 to 500 mg.

18. A pharmaceutical composition according to Claim 11, wherein the pharmaceutical composition further comprises inositol hexanicotinate, pyridoxyl phosphate, or both.

19. A pharmaceutical composition according to Claim 11, wherein the pharmaceutical composition further comprises one or more of 5-hydroxy tryptamine, tryptophan, L-phenylalanine, L-tyrosine, calcium carbonate and magnesium oxide.

20. A pharmaceutical composition according to Claim 11, wherein the pharmaceutical composition comprises *Hypericum perforatum*, *Garcinia cambogia*, inositol hexanicotinate, pyridoxyl phosphate and white willow bark extract.

21. A pharmaceutical composition according to Claim 11, wherein the pharmaceutical composition is in a form of a tablet or capsule.

22. A pharmaceutical composition, the pharmaceutical composition comprising one or both of hypericin and pseudohypericin, at least one thermogenic agent and at least one agent inhibiting lipogenesis.



# INTERNATIONAL SEARCH REPORT

In .ational Application No

PCT/US 98/12273

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 6 A61K35/78 A61K31/12

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category <sup>1</sup>	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 273 754 A (MANN MORRIS A) 28 December 1993 *see col. 4, lines 3-12 * ---	1
X	AYUGA TELLEZ ET AL.: "Study of the anorexic effect of hypericum-caprifolium Boiss." AN. R. ACAD. FARM., vol. 54, no. 2, 1988, pages 320-324, XP002078479 * see in particular p. 320 "summary"; and p. 321 l. 1-2 *	10
Y	---	1-22
Y	EP 0 599 307 A (SCHWABE WILLMAR GMBH & CO) 1 June 1994 * see claims 1,7,8; p. 6 l. 10-51 * --- -/--	1-22

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

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Date of mailing of the international search report

12/10/1998

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# INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 98/12273

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 93 08186 A (SMITHKLINE BEECHAM PLC) 29 April 1993 *see p. 9 l. 10-11 * ---	1-22
P,X	DAVIS ET AL.: "Advances and retreats in the pharmacotherapy of obesity" DRUG TOPICS, vol. 141, no. 23, 8 December 1997, pages 114-121, XP002078480 * see p. 118, left col. "Herbal fen-phen" * -----	1

# INTERNATIONAL SEARCH REPORT

Information on patent family members

Int: lional Application No

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